IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Rajeev A. JAIN et al.
Title:	RAPIDLY DISINTEGRATING SOLID ORAL DOSAGE FORM
Appl. No.:	10/667,470
Filing Date:	9/23/2003
Examiner:	Brian Yong S. Kwon
Art Unit:	1614
Confirmation Number:	9048

DECLARATION UNDER 37 C.F.R. §1.131

Sir:

I, Stephen B. Ruddy, hereby declare and state that:

1. I am a citizen of the United States of America residing at 226 Stallion Lane, Schwenksville, Pennsylvania, U.S.A.

2. Currently I am a Senior Director of NanoCrystal Technology Product Development at Elan Drug Delivery, Inc., with offices at 3500 Horizon Drive, King of Prussia, PA 19406.

3. I am a co-inventor of the invention disclosed and claimed in the above-referenced application.

4. The claimed invention directed to preparing an oral solid dose of a rapidly disintegrating nanoparticulate active agent formulation was reduced to practice prior to May 27, 1999. The work relating to preparing the claimed formulation, which occurred prior to May 27, 1999, is documented in the attached exhibits.

5. As shown in Exhibit A (Notebook No. 5611, page 55), a nanoparticulate dispersion composition, comprising 20% IC-351 (a PDE5 inhibitor) as the active agent, and 4% hydroxypropyl

methylcellulose (HPMC) and 0.2% sodium lauryl sulfate (SLS) as the surface stabilizers, and having an effective average particle size of from about 117 nm to about 124 nm, was prepared as a first step in producing a rapidly disintegrating nanoparticulate active agent composition.

6. As shown in Exhibit B (Notebook No. 5611, pages 56-57), the nanoparticulate dispersion composition described in Exhibit A was combined with mannitol (drug:mannitol ratio of 1:4), and the resulting composition was spray dried as a second step in producing a rapidly disintegrating nanoparticulate active agent composition.

7. As shown in Exhibit C (Notebook No. 5611, pages 68-69), the spray dried powder composition described in Exhibit B was combined with sodium bicarbonate, citric acid, sodium saccharin, magnesium stearate, silica, PVP K-90 and spray dried lactose. The resulting composition was then compressed into tablets on a Carver press as a final step in producing a rapidly disintegrating nanoparticulate active agent composition.

8. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

Stephen B. Ruddy

27 Jan 2011

Date

EXHIBIT A

NanoSystems™ LABORATORY NOTEBOOK NO. 5611 Page 055 of 200

Title IC-351 fast-melt taster project

(cont. from pg. 054)

Aim:- Filtering of IC-351 dispersion

Method:- 1 kg of DM-5612-116 (20% IC-351, 4% HPMC, 0.2% SLS) was filtered through a 10 µm filter cartridge. This filtered dispersion would then be mixed with mannitol and spray-dried. The particle size of this dispersion (RAJ-561M-055) was checked on Horiba LA-910.

HORIBA LA-910 for Windows(TM) Ver. 1.31

Laser scattering particle size distribution analyzer

PARTICLE SIZE MEASUREMENT DATA

ID#	[illegible] 56:05	Source	filtered through 10 um
Filename	[illegible]	Lot Numbe	[illegible]
Sample	ic351 dispersion	Test Numb	in water
Material	ic351, hpmc, sls, 1 kg.	Instrument	RAJ-5611-055

Condition

Tw(He-Ne) (LAMP)	93.2% 80.8%	Dist.Form	Std.
Agitation	2	R.R.Index	1.20-0.10i
		Circulation	3
		Sampling times	15
		Ultrasonic	: ON(60)

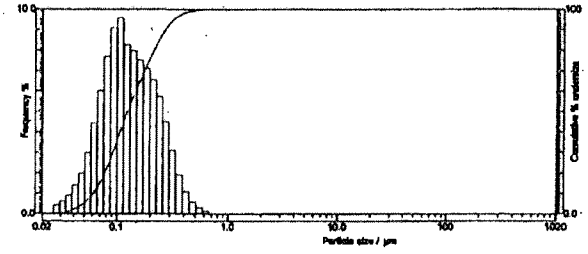
Format

Dist.base: Volume Scaling : Auto Axis : LogX - LinearY

Data

Median	: 0.124µm	SP.Area	: 557714cm²/cm³ S.D. : 0.060µm
Mode	: 0.108µm	Mean	: 0.149µm
C.V.	: 80.01%	Span	: (D 10.0-D 90.0) / D50 = 1.699

Dia. on %(90.0%) :	0.272µm	% on Dia.(0.400µm) :	98.1%
Dia. on %(80.0%) :	0.124µm	% on Dia.(0.300µm) :	93.3%
Dia. on %(95.0%) :	0.332µm	% on Dia.(0.100µm) :	35.5%
Dia. on %(80.0%) :	0.214µm	% on Dia.(0.200µm) :	76.5%
Dia. on %(70.0%) :	0.176µm	% on Dia.(1.000µm) :	100.0%



HORIBA LA-910 for Windows(TM) Ver. 1.31

Laser scattering particle size distribution analyzer

PARTICLE SIZE MEASUREMENT DATA

ID#	[illegible] 08:58	Source	filtered through 10 um
Filename	[illegible]	Lot Numbe	[illegible]
Sample	ic351 dispersion	Test Numb	in water, 1 min. son.
Material	ic351, hpmc, sls, 1 kg.	Instrument	RAJ-5611-055

Condition

Tw(He-Ne) (LAMP)	93.9% 81.6%	Dist.Form	Std.
Agitation	2	R.R.Index	1.20-0.10i
		Circulation	3
		Sampling times	15
		Ultrasonic	: ON(60)

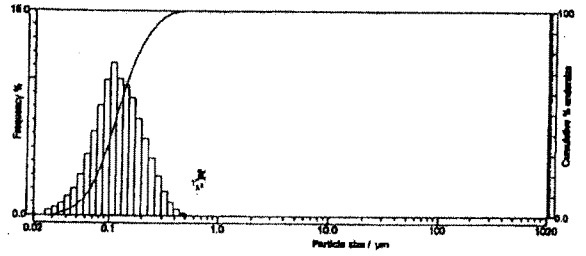
Format

Dist.base: Volume Scaling : Auto Axis : LogX - LinearY

Data

Median	: 0.117µm	SP.Area	: 582013cm²/cm³ S.D. : 0.071µm
Mode	: 0.107µm	Mean	: 0.134µm
C.V.	: 53.04%	Span	: (D 10.0-D 90.0) / D50 = 1.461

Dia. on %(90.0%) :	0.231µm	% on Dia.(0.400µm) :	99.4%
Dia. on %(80.0%) :	0.117µm	% on Dia.(0.300µm) :	96.6%
Dia. on %(95.0%) :	0.277µm	% on Dia.(0.100µm) :	37.2%
Dia. on %(80.0%) :	0.184µm	% on Dia.(0.200µm) :	84.3%
Dia. on %(70.0%) :	0.155µm	% on Dia.(1.000µm) :	100.0%



(cont. on pg. 056)

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Signature Rajeev Jain Date

Reviewed and understood by [illegible] Date

EXHIBIT B

Title IC-351 fast-melt tablet project

(cont. from pg. 055)

Aim: Spray-drying of IC-351 dispersion

Method:-

RAJ-5611-055 was mixed with mannitol and spray dried as follows:-

400 g dispersion (RAJ-5611-055) + 1280 g water + 320 g mannitol

4% drug / 16% mannitol.

The drug:mannitol ratio will be 1:4. For 320 g of mannitol was dissolved by gently heating and stirring in 1280 g of water. On cooling this soln. to room temperature, 400 g of mannitol was added and the dispersion was gently stirred (RAJ-5611-056A). This was then spray-dried using the Yamato spray dryer.

The samples were collected at various time intervals and checked for redispersibility in water.

11:45 am

~~4:05 pm~~ → RAJ-5611-056B

2:40 pm → RAJ-5611-056C

4:05 pm → RAJ-5611-056D

5:20 pm → RAJ-5611-056E

(cont. on pg. 057)

Signature Rajeev Jain Date

Reviewed and understood by Date

Title IC-351 Post-melt tablet Project

(cont. from pg. 056)

YAMATO PROCESSING INFORMATION

Product: IC-351 Date: LNB Ref: RAJ-5611-

Spray Configuration: Spray Drying Nozzle Size: Processing Gas: Nitrogen

Pump Type: Masterflex Pump Head: 7021-24 Tubing Size: 96400-14

Inlet Temperature Set Point (°C): 130 deg C Atomization Air Set Point (kgf/cm²): 2.2

Sample ID:

Time (minutes)	Pump Setting	Inlet Temp. (°C)	Outlet Temp (°C)	Drying Gas Volume (m³/min)	Pulse Jet (On/Off)	Comments / Observations
0						
11:45	9.0	128	50	0.30	—	Operation stopped and powder cleared for redispersibility (RAJ-5611-056B)
1:30 pm	10.0	128	48	0.41	—	
1:50 pm	10.0	130	51	0.39		
2:00 pm	Sprayed water for 2 minutes to clean the nozzle					
2:10 pm	10.0	130	52	0.39		
2:20 pm	Sprayed water for 2 minutes to clean the nozzle					
2:30 pm	10.0	130	53	0.40		
2:40 pm	Change Sample container & check redispersibility of powder in water (RAJ-5611-056C)					
3:00	10.0	130	54	0.39		
3:20	10.0	129	54	0.37		PSD after drying:
3:25	Sprayed water for 2 minutes to clean the nozzle					

YAMATO PROCESSING INFORMATION

Product: IC-351 Date: LNB Ref: RAJ-5611-

Spray Configuration: Spray Drying Nozzle Size: Processing Gas: Nitrogen

Pump Type: Masterflex Pump Head: 7021-24 Tubing Size: 96400-14

Inlet Temperature Set Point (°C): 130 deg C Atomization Air Set Point (kgf/cm²): 2.2

Sample ID:

Time (minutes)	Pump Setting	Inlet Temp. (°C)	Outlet Temp (°C)	Drying Gas Volume (m³/min)	Pulse Jet (On/Off)	Comments / Observations
0						
3:40 pm	10.0	130	56	0.37		
3:45 pm	Clean the nozzle by spraying water for 2 minutes					
4:00	10.0	130	58	0.36		spray water for 2 min collect sample and check redispersibility (RAJ-5611-056D)
4:05	Sprayed water and change the exhaust filter					
4:15	10.0	129	57	0.38		
4:30	10.0	130	57	0.39		sprayed water for 2 min
4:45	10.0	129	58	0.40		sprayed water for 2 min
5:00	10.0	129	59	0.40		Sprayed water for 2 min.
5:15	10.0	130	59	0.39		sprayed water for 2 min.
5:20	10.0	130	60	0.39		spraying of dispersion sample check powder for redispersibility
						PSD after drying: (RAJ-5611-056E)
5:20	Sprayed water for 5 min. to clean the nozzle					

(cont. on pg. 058)

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Signature Rajeev Jain Date

Reviewed and understood by Date

EXHIBIT C

Title IC-351 fast-melt tablet formulation

(cont. from pg. 067)

Aim:- Preparation of rapid/fast melting tablets of IC-351

Method:-

The IC-351 fast melting tablet is intended to disintegrate in less than 30 sec. The hardness of the tablet would be in the range of 1-4 KP. The ICOS SDI (RAJ-5611-060) will be used to formulate the tablets.

RAJ-5611-060 contains 19% drug (IC-351) 4.8% HPMC (pharmacoat) 76% mannitol and 0.2% SLS.

A 10 mg dose tablet is intended for this use.

The SDI would be combined with different excipients and blended, followed by light compression to give the tablets.

Sodium bicarbonate from Baker. (Lot # ~~3506-05~~ F24728) Plain
Plasdone K-90 (Povidone USP) from ISP Technologies (Lot # A70502)
Magnesium stearate from Spectrum (Lot # MT0186
Citric acid, Monohydrate from Baker (Lot # F01711)
Saccharin Sodium from Baker (Lot # 1133637)
Cab-o-sil (amorphous silica) from Cabot Corp. (Lot # IJ226)
Leo-menthol from Baker (Lot # L03628)
Spray-dried Lactose from (Lot #)

Except Silica, all the above excipients were sieved through 40 #. They were blended in different proportions.

(cont. on pg. 069)

Signature Rajeev Jain Date

Reviewed and understood by Date

Title IC-351 fast-melt tablet- project

(cont. from pg. 068)

	For 1 tablet	For 10 tablets
ICOS SDI	52.6 mg	5.260 g
Sod. bicarbonate	30 mg	3.0 g
Citric acid	30 mg	3.0 g
Saccharin Na	10 mg	1.0 g
Magnesium stearate	0.75 mg	7.5 mg
Silica	1.4 mg	14.0 mg
PVP K-90	5 mg	500 mg
Spray-dried lactose	20.25 mg	2.025 g
	150 mg	15.00 g

Except silica and mag. stearate all the above excipients were blended in a V-blender from Patterson-Kelley for 30 min. Finally a mixture of silica and magnesium stearate was added & the blending continued for 2 more min. The resultant powder (RAJ-5611-069) was ready for compression.

Tablets weighing 150 mg were prepared using the automated Carver press and RAJ-5611-069.

The press was set-up for compression force of 700 lb; pump speed, 15 %; dwell time, 0 sec. However, the actual compression force during compression was found to be 800 psi. The tablets had hardness in the range of 3-4 kP. However the tablets exhibited tremendous capping and sticking to the punches. This could be due to the use of PVP K-90.

(cont. on pg. 070)

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Signature Rajeev Jain Date

Reviewed and understood by Date